The claims in the application as filed have been canceled and new claims 28-54 have been added to more particularly point out and distinctly claim that which applicants regard as the invention. The new claims are fully supported by the claims as filed and by the specification. In particular, support for new claims 29-55 is set forth in the following table:

New Claims	Support
28.	Claim 1 as filed; p. 27, l. 9 (coding sequence); at p. 2, l. 4 and p. 5, ll. 19-20 (enzymatically active matrix degrading enzyme (MDE) that degrades an extracellular matrix component); p. 6, ll. 11-12 (regulatable promoter); p. 13, ll. 6-8 (promoter that is responsive to a transcriptional repressor or activator polypeptide); p. 37, l. 1, p. 6, ll. 4-5, p. 13, ll. 3-4 (chondrocyte tissue-specific promoter); p. 13, l. 1, p. 16, ll. 12-15 (expression repressed throughout embryonic, fetal, and early postnatal development); p. 6., l. 5-6, p. 18, ll. 9-11 (MDE expression results in a phenotypic change characteristic of osteoarthritis).
29.	p. 2, Table 1 and p. 5, ll. 23-24.
30.	p. 12, l. 8.
31.	p. 12, l. 13.
32.	claim 7 as filed; p. 12, ll. 16-18.
33.	claim 8 as filed.
34.	claim 9 as filed.

35.	p. 13, l. 10.
36.	p. 14, l. 21.
37.	claim 11 as filed; p. 14, ll. 21-22
38.	claim 12 as filed
39.	claim 15 as filed; p. 16, l. 2.
40. (also 43, 45, 48, and 51)	p. 18, ll. 13-15; p. 19, ll. 11-18; p. 21, ll. 5-6.
41.	p. 27, l. 9 (coding sequence); p. 12, ll. 8-12 (constitutively active MMP); p.3, ll. 4-5, p. 11, ll. 5-6 (degrades Type II collagen) p. 6, ll. 11-12; p. 13, ll. 6-8 and 19; (tetracycline regulatable promoter); p. 13, l. 19 (tetracycline repressor polypeptide); p. 37, l. 1; p. 6, ll. 4-5; p. 13, ll. 3-4 (chondrocyte tissue-specific promoter); p. 13, l. 1 and p. 16, ll. 12-15 (expression repressed throughout embryonic, fetal, and early postnatal development); p. 18, ll. 9-11 (MMP expression results in phenotypic change characteristic of osteoarthritis).
42.	claim 16 as filed; p. 17, l. 24 to p. 18, l. 2.
44. (also 46 and 49)	claims 22-24 as filed; p. 18, ll. 16-21.
47. (also 50)	p. 41, l. 6.

52-54 claims 25-27 as filed; p. 20, l. 13 to p. 21, l. 2.

SUMMARY OF POINTS

Based on the grounds for rejection in the outstanding Final Office Action in the '689 parent application, and the discussion at the interview in the '689 parent application conducted on May 17, 2000, applicants submit that there are no issues with respect to patentability of the specific transgenic mice exemplified in this application. However, as discussed at the interview, such a limited claim scope denies the protection to which this discovery is entitled: any transgenic animal that expresses an enzymatically active matrix degrading enzyme under control of an inducible promoter and a tissue-specific promoter, and, when induced to express the enzymatically active matrix degrading enzyme, develops phenotypic changes characteristic of osteoarthritis. Applicants wish to emphasize the following points in support of patentability of the invention as presently claimed:[1]

- Enzymatically active matrix degrading enzymes that degrade extracellular matrix components are well known. Applicants have established this in the file history of the application as follows:

  Specification: pages 2-3; pages 11-12.

  Additional evidence: Second Neuhold Declaration, paragraph 8.

- Expression of coding sequences under control of regulatable promoters that are responsive to a transcriptional repressor or activator polypeptide in transgenic

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[1] Applicants refer herein to the Declaration of Lisa A. Neuhold, Ph.D. Under 37 C.F.R. § 1.132 filed April 6, 1999 (the Neuhold Declaration; copy attached as Exhibit A), the preliminary Amendment filed by hand on February 18, 2000 (the Preliminary Amendment; copy attached as Exhibit B) and the Second Declaration of Lisa A. Neuhold, Ph.D. Under 37 C.F.R. § 1.132 filed August 30, 2000 (the Second Neuhold Declaration; copy attached as Exhibit C), filed in the '689 parent application.

animals is well known. Applicants have established this in the file history of this application as follows:

Specification: pages 12-15 and pages 16-18.

Additional Evidence: Exhibits A, B, C, D, and E to Preliminary Amendment; Second Neuhold Declaration, paragraph 6.

- Tissue specific expression of transgenes in transgenic animals is well known. Applicants have established this in the file history of this application as follows:

  Specification: pages 15-16 and 17-18.

  Additional Evidence: Neuhold Declaration, paragraph 6; Second Neuhold Declaration, paragraph 7 and Tab 2.

- Transgenic nonhuman mammals, particularly mice, rats, and rabbits, are well known and prepared routinely by ordinary research scientists at the time this invention was made. It is also a known and accepted that, as with every other experimental system in biology such as cloning and hydridomas, not every transgenic embryo will yield a transgenic animal with the desired characteristics, but that routine screening and selection techniques will provide such an animal as claimed. Applicants have established this extensively in the file history of this application as follows:

  Specification: pages 22-26.

  Additional Evidence: Second Neuhold Declaration, paragraph 9 and Tab 4.

- Phenotypic characteristics of osteoarthritis (degenerative bone disease), as developed in the transgenic animals of the invention are well-known. Applicants have established this in the file history of the application as follows:

    Specification: pages 18-20, 21 and 45.
    Additional Evidence: Neuhold Declaration, paragraphs 6, 11, 13 and 14; Exhibits F, G, H, and I to the Preliminary Amendment; Second Neuhold Declaration, paragraph 10.

- The totality of the evidence of record in the file history of this application establishes that the claimed transgenic mammals, particularly the claimed transgenic mice and rats, can be generated and induced to develop one or more phenotypic characteristics of osteoarthritis. These transgenic animals thus serve as useful models for studying the progression and evaluating therapies for this disease. Applicants have established these features of the invention throughout the file history of the application as set forth and as follows:

    Specification: pages 1, 5-7, 18-20, 21 and 45.
    Additional Evidence: Neuhold Declaration, paragraph13; Second Neuhold Declaration, paragraph 11.

THE SPECIFICATION ENABLES THE CLAIMED INVENTION

In the '689 application, the Examiner had rejected claims 29-55 under 35 U.S.C. § 112, first paragraph, contending that while being enabling only for MMP13* (SEQ ID NO:1) linked to any regulatable promoter, *e.g.*, tet07 promoter + tet repressor and VP16 activator,

linked to Type II collagen promoter where a mouse is given the regulatory compound, *e.g.*, tetracycline until adulthood, the specification does not provide enablement for a mammal.

Applicants respectfully traverse this rejection. For the reasons advanced above in the accompanying Second Neuhold Declaration, the specification enables claims to mammals. In particular, ". . . contrary to the examiner's assertions, as of 1996 creation of transgenic mammals required no more than ordinary technical efforts – indeed, technical efforts with shortcomings that are readily overcome" (Neuhold Declaration, paragraph 9).[2] All of these techniques are set forth in the specification at pages 22-26.

Notably, the present invention discloses, *inter alia*, microinjection of zygotes, viral integration, and transformation of embryonic stem cells "as methods for introducing transgenes into animals (specification, page 23, lines 11-12). "Microinjection of zygotes in the preferred method" (page 23, line 13; see, page 23, line 13 to page 24, line 3), which the specification exemplifies (see page 38, lines 13-19)[3] for the reasons discussed in greater detail below, the state of the art at the time this invention was made was much farther advanced than the Examiner allows, and the Examiner's contention is incorrect.

The Examiner further contended that the specification does not teach how to get phenotype with any other regulating system. As discussed during the interview and set forth in the accompanying Second Neuhold Declaration at paragraph 6, the regulatable expression systems described in the specification are well established and well known in the art. As set forth above, applicants have submitted numerous references further supporting enablement of this aspect of the invention. The Examiner appeared to agree with this position at the interview and in the Final Office Action. Accordingly, this basis for the rejection is mooted.

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[2] The '689 Final Office Action does not address this fact.

[3] The Examiner's focus on ES-cell approaches to creation of transgenic animals seems particularly misplaced in view of these facts.

The Examiner also contended that the specification does not teach how to get other phenotypes. Applicants disagree; the record as set forth above and the Second Neuhold Declaration (paragraphs 10 and 11) firmly establishes that the transgenic mammals, and especially rodents, of the invention, upon expression of the matrix degrading enzyme, develops a phenotypic change characteristic of osteoarthritis.

The Examiner contended that it is not clear whether other extracellular matrix degrading enzymes would achieve the claimed phenotype. Applicants respectfully disagree. The specification sets forth a plethora of matrix degrading enzymes (pages 2-3); the Examiner has provided no evidence or documentation to substantiate doubts that other MDEs would achieve this phenotype. It is uncontroverted that other Type II collagenase enzymes, such as MMP-1, MMP-8, and MMP-13, would (see claim 41). The Examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). MPEP § 2164.04. The Examiner clearly failed to meet this burden here.[4] In contrast, Applicants have more than met theirs: in addition to the express disclosure of the specification (see pages 2-3 and 11-12), they have further addressed this issue in the interview and by Rule 132 Declaration (*see* the Second Neuhold Declaration, paragraph 8). Thus, this rejection is overcome and should be withdrawn. Claim 41 particularly addresses these concerns by reciting a constitutively active collagen II-specific MMP.

The Examiner asserted that the invention is unpredictable with regard to phenotype. However, the evidence of record in the specification (pages 41-44), the Neuhold Declaration (paragraphs 9, 11, 13, 14, and 15), and the Second Neuhold Declaration (paragraphs 10 and 11) firmly establish that the transgenic animals of the invention demonstrate the claimed phenotypic change, *i.e.*, one or more characteristics of osteoarthritis.

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[4] The '689 Final Office Action does not address this defect.

The Examiner also asserted that non-mutated MMP genes are not enabled. As these proteins, and methods for activating them, are extremely well known in the art (as agreed at the interview), which is specifically established on pages 2-3 of the specification, Applicants submit that this rejection is obviated and should be withdrawn. Furthermore, this rejection does not properly apply to claim 41.

The Examiner further contended that the specification is only enabled for MMP13* and exemplified phenotype. For the reasons set forth above, Applicants submit that the specification broadly enables transgenic mammals that express any MDE in a tissue specific, temporally regulated fashion. Furthermore, as the exemplified phenotype is a phenotypic change characteristic of osteoarthritis, which includes cartilage degradation (Second Neuhold Declaration, paragraphs 10 and 11), the specification clearly enables this aspect of the claimed invention as well. Thus, these bases for rejecting the claims are obviated and should be withdrawn.

The Examiner contended that the specification is not enabled for any joint specific promoter and should recite only a Type II collagen promoter. As discussed during the interview and set forth in the Second Neuhold Declaration (paragraph 7), the specific promoter employed to achieve tissue specific expression does not make any difference, as one of ordinary skill in the art would readily appreciate. A number of issued patents that cover transgenic animals establish tissue-specific expression is sufficiently enabled for expression of a transgene, because the actual tissue specific promoter is usually of no moment. Moreover, it is proper in a patent for a transgenic animal to claim the promoter by virtue of its tissue specificity rather than identity. *See* U.S. Patent Nos. 5,625,124 (claim 1: "gut epithelial cell specific promoter"); 5,880,327 (claim 1: "a mammary-gland specific promoter"); 5,917,123 (claim 1: "a cardiac-specific regulatory region"); 6,028,245 (claim 1: "a promoter that drives expression of the transgene in skin")

(attached as Exhibit 2). In view of the foregoing, the Examiner's basis for this rejection is obviated and should be withdrawn.[5]

The Examiner cited references detailing expression in other mammals as support for argument that the specification does not enable non-human mammals besides mouse. Applicants respectfully take issue with these citations on two grounds. First, they support the opposite conclusion: that the claimed transgenic animals are enabled. Second, these references do not adequately support the rejection. Applicants submit that the Examiner has not carried this burden where the support (1) generally refers to the generic technology; (2) addresses questions related to economics and commercialization, not § 112, first paragraph; (3) contains no information specifically relevant to the claimed invention; and (4) is out of date (none of the references cited by the Examiner have publication dates later than 1996; one was published in 1988; in a rapidly evolving field such as transgenic animals, only the most current references from the time the invention was made have any bearing). *Cf. In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993) (applying references directly addressing the claims in issue to establish lack of enablement).[6]

In particular, the Wall reference reports that 6000 papers describe transgenic animals, mostly mice, to answer research questions (pages 58, 60, and 61). Wall states that ". . . genes can . . . be modified to function very differently than they do in their native form (gene products, tissue specificity, and timing of expression can be altered)" (page 58). In other words, Wall specifically states that the features of Applicants' invention can be achieved. Wall does concede that transgenic farm animals are costly (mostly because it takes many attempts to yield the desired transgenic animal) (see page 60), however, economic issues are irrelevant to

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[5] The '689 Final Office Action fails to address any of these issues.

[6] The '689 Final Office Action does not address any of these issues, or Applicants' contention that the references clearly support enablement, as discussed further.

enablement. How is it possible that a reference acknowledging such an abundance of research papers on transgenic animals, manipulation of expression, and at least 1% efficiency of obtaining the desired transgenic animal (much higher, one might add, than the likelihood of obtaining a desired monoclonal antibody or even cloning a gene) calls into question enablement of this invention? On the contrary, Applicants might very well (and here do) cite such a reference to support the routine nature of generating experimental transgenic animals for disease models.

The Ebert reference (from 1988) reports success ("Transgenic pigs carrying this fusion gene had elevated levels of circulating human somatrotropin"; page 277). Applicants submit that the presence of failures is irrelevant in the face of success. The entire history of biology is one of selecting and screening for successes from the much more abundant failures. *See In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) (enablement of broad monoclonal antibody claims despite the large number of trials necessary to obtain the operative antibody).

Mullins and Mullins, like Wall, report that transgenic technology, including ES technology, is well established (page S37). Time and cost, issues irrelevant to enablement, limit the desirability of pronuclear injection in larger mammals. No matter, as pointed out in the specification, ES technology is an alternative. In any event, the fact that pronuclear injection is less efficient, and therefore economically undesirable, fails to establish that it does not work. On the contrary, nothing in Mullins and Mullins supports such a conclusion. In any event, this paper reports on a number of successful non-murine transgenic animal models (see page S38).

Finally, the Overbeck reference shows that different transgenic animals will demonstrate different levels of expression. Regulatory sequences help avoid variability (see page 97), but this makes little difference: variability ranges from one extreme to another, from no phenotypic change to the desired change. The Examiner contends that this establishes unpredictability. Applicants disagree. This establishes predictability of two things: there will be failures, and there will also be successes. By selecting the successes, which is routine, one

achieves the desired transgenic animals. Indeed, applicants themselves had failures, among which successful animals were obtained (see page 43 of the specification).

In short, the Examiner's grounds for rejection are in error given the advanced state of the art, including general recognition of enablement of transgenic animals (irrespective of whether or not they are cost effective), widespread knowledge of regulatable expression systems, the understanding in the art of tissue-specific expression, and the number of well known extracellular matrix degrading enzymes from which to choose. The present invention is broadly enabled, and the Examiner has not met his burden of challenging enablement with reasonable evidence. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph is in error and should be withdrawn.

CONCLUSION

Because the claims of this application, which is a continuing application of the '689 application, are drawn to the same invention claimed in the earlier application and would have been properly [sic, procedurally][7] finally rejection on the grounds of record in the next Office Action if they had been entered in the '689 application. Accordingly, a Final Rejection is appropriate as a First Office Action in this Continuation application. MPEP § 706.07(b) (Rev. 1, Feb. 2000). Accordingly, if the Examiner persists in rejecting these claims, applicants believe a Final Rejection is appropriate and necessary to permit appeal.

Applicants respectfully request entry of the foregoing amendments and remarks as well as the amendments and Rule 132 Declarations from the '689 application in the file history of this application. In view of the foregoing amendments and remarks, applicants submit that the

[7] Applicants use the term properly in a procedural context, and do not agree with or concede the rejections in '689.

claims meet all the statutory requirements for patentability. If the Examiner has any other concerns, he is invited to contact the undersigned by telephone. Allowance or Final Rejection of the claims is earnestly solicited.

Respectfully submitted,

Date: November 20, 2000

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